1   We claim:

2   1.   A composition comprising:

3   an RNAi-inducing entity, wherein the RNAi-inducing entity is targeted to a

4   target transcript; and

5   a delivery agent selected from the group consisting of: cationic polymers,

6   modified cationic polymers, peptide molecular transporters, surfactants suitable for

7   introduction into the lung, liposomes, non-cationic polymers, modified non-cationic

8   polymers, bupivacaine, and chloroquine.

9   2.   The composition of claim 1, wherein the delivery agent comprises a delivery-

10   enhancing moiety to enhance delivery to a cell of interest.

11   3.   The composition of claim 2, wherein the delivery-enhancing moiety comprises an

12   antibody, antibody fragment, or ligand that specifically binds to a molecule

13   expressed by the cell of interest.

14   4.   The composition of claim 3, wherein the cell of interest is a respiratory epithelial

15   cell.

16   5.   The composition of claim 2, wherein the delivery-enhancing moiety comprises a

17   moiety selected to reduce degradation, clearance, or nonspecific binding of the

18   delivery agent.

19   6.   The composition of claim 1, wherein a disease or clinical condition, or a symptom

20   thereof, is associated with excessive expression or inappropriate expression of the

21   target transcript or inappropriate or excessive functional activity of a polypeptide

22   encoded by the target transcript.

23   7.   The composition of claim 1, wherein the RNAi-inducing entity comprises an siRNA.

24   8.   The composition of claim 1, wherein the RNAi-inducing entity comprises an

25   shRNA.

26   9.   The composition of claim 1, wherein the RNAi-inducing entity comprises a

27   lentivirus.

1   10.   The composition of claim 1, wherein the RNAi-inducing entity comprises an RNAi-

2   inducing vector.

3   11.   The composition of claim 10, wherein:

4   the vector comprises a nucleic acid comprising a promoter for RNA

5   polymerase III.

6   12.   The composition of claim 11, wherein:

7   the promoter is a U6 or H1 promoter.

8   13.   The composition of claim 1, wherein the RNAi-inducing entity comprises a viral

9   vector.

10   14.   The composition of claim 1, wherein the RNAi-inducing entity comprises a lentiviral

11   vector.

12   15.   The composition of claim 1, wherein the RNAi-inducing entity comprises a DNA

13   vector.

14   16.   The composition of claim 1, wherein:

15   the RNAi-inducing entity is an siRNA or shRNA targeted to a target

16   transcript or an RNAi-inducing vector whose presence within a cell results in

17   production of an siRNA or shRNA targeted to a target transcript, wherein the siRNA

18   or shRNA comprises a portion that is perfectly complementary to a region of the

19   target transcript, wherein the portion is at least 15 nucleotides in length.

20   17.   The composition of claim 1, wherein:

21   the RNAi-inducing entity is an siRNA or shRNA targeted to a target

22   transcript or an RNAi-inducing vector whose presence within a cell results in

23   production of an siRNA or shRNA targeted to a target transcript, wherein the siRNA

24   or shRNA comprises a portion that is perfectly complementary to a region of the

25   target transcript, wherein the portion is approximately 19 nucleotides in length.

26   18.   The composition of claim 1, wherein:

27   the RNAi-inducing entity is an siRNA or shRNA targeted to a target

28   transcript or an RNAi-inducing vector whose presence within a cell results in

1   production of an siRNA or shRNA targeted to a target transcript, wherein the siRNA

2   or shRNA comprises a portion that is perfectly complementary to a portion of the

3   target transcript, with the exception of three or fewer nucleotides, wherein the

4   portion is at least 15 nucleotides in length.

5   19.   The composition of claim 1, wherein:

6   the RNAi-inducing entity is an siRNA or shRNA targeted to a target

7   transcript or an RNAi-inducing vector whose presence within a cell results in

8   production of an siRNA or shRNA targeted to a target transcript, wherein the siRNA

9   or shRNA comprises a portion that is perfectly complementary to a portion of the

10   target transcript, with the exception of three or fewer nucleotides, wherein the

11   portion is approximately 19 nucleotides in length.

12   20.   The composition of claim 1, further comprising at least one pharmaceutically

13   acceptable diluent, excipient, or carrier.

14   21.   The composition of claim 1, wherein:

15   the composition comprises a plurality of different siRNAs, shRNAs, or

16   RNAi-inducing vectors whose presence within a cell results in production of a

17   plurality of different siRNAs or shRNAs, wherein the siRNAs or shRNAs are

18   targeted to a single target transcript.

19   22.   The composition of claim 1, wherein:

20   the composition comprises a plurality of different siRNAs, shRNAs, or

21   RNAi-inducing vectors whose presence within a cell results in production of a

22   plurality of different siRNAs or shRNAs, wherein the siRNAs or shRNAs are

23   targeted to different target transcripts.

24   23.   The composition of claim 1, wherein the delivery agent is selected from the group

25   consisting of cationic polymers and modified cationic polymers.

26   24.   The composition of claim 23, wherein the cationic polymer is selected from the

27   group consisting of polylysine, polyarginine, polyethyleneimine,

28   polyvinylpyrrolidone, chitosan, and poly(β-amino ester) polymers.

29   25.   The composition of claim 24, wherein the cationic polymer is polyethyleneimine.

1   26.   The composition of claim 24, wherein the cationic polymer is selected from the
2   group consisting of poly(β-amino ester) polymers.

3   27.   The composition of claim 24, wherein the modified cationic polymer incorporates a
4   modification selected to reduce the cationic nature of the polymer.

5   28.   The composition of claim 27, wherein the modification comprises substitution with a
6   group selected from the group consisting of: acetyl, imidazole, succinyl, and acyl.

7   29.   The composition of claim 24, wherein between 25% and 75% of the residues of the
8   modified cationic polymer are modified.

9   30.   The composition of claim 29, wherein approximately 50% of the residues of the
10   modified cationic polymer are modified.

11   31.   The composition of claim 23, wherein the RNAi-inducing entity comprises an
12   siRNA.

13   32.   The composition of claim 23, wherein the RNAi-inducing entity comprises an
14   shRNA.

15   33.   The composition of claim 23, wherein the RNAi-inducing entity comprises an
16   RNAi-inducing vector.

17   34.   The composition of claim 23, wherein the RNAi-inducing entity comprises a DNA
18   vector.

19   35.   The composition of claim 23, wherein the RNAi-inducing entity comprises a viral
20   vector.

21   36.   The composition of claim 23, wherein the RNAi-inducing entity comprises a
22   lentiviral vector.

23   37.   The composition of claim 23, wherein the RNAi-inducing entity comprises a
24   lentivirus.

1   38.   A method of inhibiting a target transcript in a mammalian subject comprising
2   administering the composition of claim 23 to the respiratory system of a subject by
3   introducing the composition into the vascular system of the subject.

4   39.   The method of claim 38, wherein the solid organ is the lung.

5   40.   The method of claim 38, wherein the composition is administered by intravenous
6   injection.

7   41.   The method of claim 38, wherein the composition is administered using a
8   conventional fluid delivery technique.

9   42.   The method of claim 38, wherein the RNAi-inducing entity comprises an siRNA.

10   43.   The method of claim 38, wherein the RNAi-inducing entity comprises an shRNA.

11   44.   The method of claim 38, wherein the RNAi-inducing entity comprises an RNAi-
12   inducing vector.

13   45.   The method of claim 38, wherein the RNAi-inducing vector comprises a DNA
14   vector.

15   46.   The method of claim 38, wherein the RNAi-inducing vector comprises a viral vector.

16   47.   The method of claim 38, wherein the RNAi-inducing vector comprises a lentiviral
17   vector.

18   48.   The method of claim 38, wherein the RNAi-inducing vector comprises a lentivirus.

19   49.   A method of treating or preventing a disease or clinical condition associated with
20   overexpression or inappropriate expression of a transcript or excessive functional
21   activity of a polypeptide encoded by the transcript comprising the step of delivering
22   the composition of claim 23 to a solid organ or tissue of a subject at risk of or
23   suffering from the disease or clinical condition by introducing the composition into
24   the vascular system of the subject.

25   50.   The composition of claim 1, wherein the delivery agent comprises a surfactant
26   suitable for introduction into the lung.

1   51.   The composition of claim 50, wherein the surfactant comprises 10-20% protein and
2   80-90% lipid by weight both based on the whole surfactant, which lipid consists of
3   about 10% neutral lipid and of about 90% phospholipid.

4   52.   The composition of claim 50, wherein the surfactant is derived from animal tissue or
5   lung lavage.

6   53.   The composition of claim 50, wherein the surfactant is synthetic.

7   54.   The composition of claim 50, wherein the surfactant is approved by the U.S. Food
8   and Drug Administration.

9   55.   The composition of claim 50, wherein the surfactant is Infasurf®, Survanta®, or
10   Exosurf®.

11   56.   The composition of claim 50, wherein the RNAi-inducing entity comprises an
12   siRNA

13   57.   The composition of claim 50, wherein the RNAi-inducing entity comprises an
14   shRNA.

15   58.   The composition of claim 50, wherein the RNAi-inducing entity comprises an
16   RNAi-inducing vector.

17   59.   The composition of claim 50, wherein the RNAi-inducing entity comprises a DNA
18   vector.

19   60.   The composition of claim 50, wherein the RNAi-inducing entity comprises a viral
20   vector.

21   61.   The composition of claim 50, wherein the RNAi-inducing entkty comprises a
22   lentiviral vector.

23   62.   The composition of claim 50, wherein the RNAi-inducing entity comprises a
24   lentivirus.

1 63. A method of inhibiting a target transcript in a mammalian subject comprising
2 administering the composition of claim 50 to the respiratory system of a subject by
3 inhalation or intranasal delivery.

4 64. The method of claim 63, wherein the RNAi-inducing entity comprises an siRNA.

5 65. The method of claim 63, wherein the RNAi-inducing entity comprises an shRNA.

6 66. The method of claim 63, wherein the RNAi-inducing entity comprises an RNAi-
7 inducing vector.

8 67. The method of claim 63, wherein the RNAi-inducing entity comprises a viral vector.

9 68. The method of claim 63, wherein the RNAi-inducing entity comprises a lentiviral
10 vector.

11 69. The method of claim 63, wherein the RNAi-inducing entity comprises a lentivirus.

12 70. The method of claim 63, wherein the RNAi-inducing entity comprises a DNA
13 vector.

14 71. A method of treating or preventing a disease or clinical condition associated with
15 overexpression or inappropriate expression of a target transcript or excessive
16 functional activity of a polypeptide encoded by the target transcript comprising the
17 step of administering the composition of claim 50 to the respiratory system of a
18 subject at risk of or suffering from the disease or clinical condition by inhalation or
19 intranasal delivery.

20 72. The composition of claim 1, wherein the delivery agent is a peptide molecular
21 transporter.

22 73. The composition of claim 72, wherein the peptide molecular transporter is an
23 arginine-rich peptide containing at least 4 arginine residues.

24 74. The composition of claim 72, wherein the RNAi-inducing entity comprises an
25 siRNA.

1 75. The composition of claim 72, wherein the RNAi-inducing entity comprises an
2   shRNA.

3 76. The composition of claim 72, wherein the RNAi-inducing entity comprises an
4   RNAi-inducing vector.

5 77. The composition of claim 72, wherein the RNAi-inducing entity comprises a viral
6   vector.

7 78. The composition of claim 72, wherein the RNAi-inducing entity comprises a
8   lentiviral vector.

9 79. The composition of claim 72, wherein the RNAi-inducing entity comprises a
10   lentivirus.

11 80. The composition of claim 72, wherein the RNAi-inducing entity comprises a DNA
12   vector.

13 81. A method of inhibiting expression of a target transcript in a mammalian subject
14   comprising the step of administering to the subject a composition comprising:
15   (i) an RNAi-inducing entity targeted to the target transcript; and
16   (ii) a delivery agent selected from the group consisting of: cationic polymers,
17   modified cationic polymers, peptide molecular transporters, surfactants suitable for
18   introduction into the lung, lipids, liposomes, lipopolyplexes, non-cationic polymers,
19   modified non-cationic polymers, bupivacaine, and chloroquine.

20 82. The method of claim 81, wherein adminstration of the composition inhibits
21   expression of the target transcript in the lung.

22 83. The method of claim 81, wherein administration of the composition inhibits
23   expression of the target transcript in at least one tissue or organ other than the lung,
24   in addition to, or instead of, inhibiting the transcript in the lung.

25 84. A method of treating or preventing a disease or condition associated with
26   overexpression or inappropriate expression of a transcript or inappropriate or
27   excessive expression or activity of a polypeptide encoded by the transcript, the
28   method comprising steps of:

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1   (a) providing a subject at risk of or suffering from a disease or condition

2 associated with overexpression or inappropriate expression of a transcript or

3 inappropriate or excessive expression or activity of a polypeptide encoded by the

4 transcript; and

5   (b) administering to the subject a composition comprising:

6   (i) an RNAi-inducing entity targeted to the target transcript; and

7   (ii) a delivery agent selected from the group consisting of: cationic

8 polymers, modified cationic polymers, peptide molecular transporters, surfactants

9 suitable for introduction into the lung, lipids, liposomes, non-cationic polymers,

10 modified non-cationic polymers, bupivacaine, and chloroquine.

11 85.   The method of claim 84, wherein the composition is administered by inhalation or

12 intranasally.

13 86.   The composition of claim 85, wherein the composition is administered as an aerosol.

14 87.   The method of claim 84, wherein the composition is administered intravenously.

15 88.   The method of claim 87, wherein the composition is administered using a

16 conventional intravenous administration technique.

17 89.   The method of claim 84, wherein the delivery agent comprises a delivery enhancing

18 moiety to enhance delivery to a cell of interest.

19 90.   The method of claim 89, wherein the delivery-enhancing moiety comprises an

20 antibody, antibody fragment, or ligand that specifically binds to a molecule

21 expressed by the cell of interest.

22 91.   A composition comprising:

23   an analog of an siRNA or shRNA whose presence within a cell results in

24 production of an siRNA or shRNA, wherein the siRNA or shRNA is targeted to a

25 target transcript, wherein the analog differs from the siRNA or shRNA in that it

26 contains at least one modification that results in increased stability, enhanced

27 absorption, or enhanced cellular entry of the siRNA or shRNA; and

28   a delivery agent selected from the group consisting of: cationic polymers,

29 modified cationic polymers, peptide molecular transporters, surfactants suitable for

1 introduction into the lung, liposomes, non-cationic polymers, modified non-cationic

2 polymers, bupivacaine, and chloroquine.

3 92. The composition of claim 91, wherein:

4   the modification modifies a base, a sugar, or an internucleoside linkage.

5 93. The composition of claim 91, wherein:

6   the modification is not a nucleotide 2' modification.

7 94. The composition of claim 91, wherein:

8   the modification is a nucleotide 2' modification.

9 95. The composition of claim 91, wherein:

10   the analog differs from the siRNA or shRNA in that at least one

11 ribonucleotide is replaced by a deoxyribonucleotide.

12 96. A method of inhibiting a target transcript in a subject comprising administering the

13 composition of claim 91 to the subject, wherein the RNAi-inducing agent is targeted

14 to the target transcript.

15 97. A method of treating or preventing a disease or condition associated with

16 overexpression or inappropriate expression of a transcript or inappropriate or

17 excessive expression or activity of a polypeptide encoded by the transcript, the

18 method comprising steps of:

19   (a) providing a subject at risk of or suffering from a disease or condition

20 associated with overexpression or inappropriate expression of a transcript or

21 inappropriate or excessive expression or activity of a polypeptide encoded by the

22 transcript; and

23   (b) administering the composition of claim 91 to the subject, wherein the

24   RNAi-inducing agent is targeted to the target transcript.

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